

Remarks

The pending claims are 1-2, 8, 11, 15-16, 18-19, 21-35, 37, 42-43, 45-47, 50, 52-54, 56, 60, 62, 68, 70, 76-77, and 83-91. Claims 8, 11, 15-16, 18-19, 21, 23, 26-34, 37, 42, 53, and 83 have been withdrawn from consideration.

Claims 43, 45-47, 50, 52, 54, 56, 60, 62, 68, 70, 76-77, and 84-89 have been rejected under 35 U.S.C. §112 (1st paragraph) as failing to comply with the enablement requirement. Claims 1-2, 22, 35, and 90-91 have been rejected under 35 U.S.C. §103(a) as unpatentable over Yamamori, *et al.*, JP 2001-139550 ("Yamamori"). Claims 24 and 25 have been rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 5,705,521 to Abraham, *et al.* ("Abraham"). Reconsideration is requested.

Explanation of the Amendments

Specification

The specification at page 71, line 5, contains an obvious error in the definition of compounds of Formula VIII. The symbol "R⁵" in these definitions should be "L." Applicant believes that this error is an obvious error and that the rectification of the error is obvious in the sense that anyone would immediately realize that nothing else could have been intended other than what is offered as rectification. In addition to appearing at page 71, line 5 (and in claim 27, discussed below), Formula VIII also appears at page 79, line 16 and in claim 32 as originally filed at page 132, line 12. In both of these other instances, the designation "L" is correctly employed in the definition of the electrophilic reactive center for the Formula VIII compounds. Thus, the error at page 71 is an obvious error. It is also apparent that the rectification of the error is obvious in the sense that anyone would immediately realize that nothing else could have been intended other than what is offered as rectification. Moreover, the error at page 71, line 5, wherein the symbol L is incorrectly replaced with R⁵, is inconsistent with all of the other definitions of R⁵ throughout the specification. Furthermore, the process disclosed at page 71, line 5 and claimed in claim 27 is a process of making a compound of Formula Ic. R⁵ for

compounds of Formula Ic is defined at page 83, line 5 as being the same as the definition of R⁵ for Formula I compounds, which R⁵ definition is disclosed in the specification, at page 31, line 18-25. The definition of R⁵ for the Formula VIII precursor to a Formula Ic compound cannot reasonably be different from the definition of R⁵ for the product of Formula Ic formed by the disclosed process. Again this error is an obvious error and the rectification of the error is obvious in the sense that anyone would immediately realize that nothing else could have been intended other than what is offered as rectification.

Claims

New claims 92 and 93 are added directed to specific compounds, supported by Examples 3-10 and 11, respectively, in the specification, taken from claim 22 as originally filed. Similarly, new claim 94, depending from claim 21 (that ultimately depends from claim 8), is added directed to specific compounds, taken from claim 22 as originally filed.

Claim 8 is amended to include the group "-OR⁴" in the term "R^{3m}", which finds support in the specification at p. 19, line 20, which is also the elected species.

Claim 15 is amended merely to correct a clerical error by removing a redundant limitation.

Claim 22 is amended by removal of several species, most of which have been included in new claims 92-94.

Claim 27 is amended merely to correct two clerical errors, namely, the symbol "R⁵" is the definitions of the compound of formula VIII should be "L," and the term "R⁶" should be "R⁵." Support for the correction of the first error is discussed above in the explanation for the corresponding amendment to the specification. Support for the correction of the second error can be found in claim 21 as originally filed, from which claim 27 depends.

Claims 43, 50, 54, 62, 68 and 76 are amended to include specific compounds and specific cancers, supported by Examples 1 to 15 in the specification.

Claims 45-47, 52, 54, 56, 60, 62, 68, 70 and 76-77 are cancelled.

Claim 83 is amended merely to correct a clerical error by replacement of the term "Q" with lower case "q." Although a skilled person would consider this an obvious typographical error, support for this amendment can be found in claim 21 as originally filed, from which the claim depends.

Claims 84-89 are cancelled.

All claims cancelled herein are cancelled without prejudice to the filing of one or more continuing applications.

Response to the Rejections

(1) Rejection of Claims 43, 45-47, 50, 52, 54, 56, 60, 62, 68, 70, 76-77, and 84-89 under 35 U.S.C. §112 (1st paragraph) enablement requirement.

The Examiner has maintained the rejection of claims 43, 45-47, 50, 52, 54, 56, 60, 62, 68, 70, 76-77, and 84-89 under 35 U.S.C. §112 as allegedly containing subject matter which is not described in the specification in such a way as to enable a person skilled in the art to make and/or use the invention.

The Examiner has acknowledged on p. 3 of the Office Action that Applicants in Table 5 have presented data demonstrating that the claimed compounds are effective against some cell lines. While not conceding agreement with the Examiner's conclusions regarding enablement, but in an effort to advance prosecution, claims 43 and 50 have been amended to recite administration of compounds of Examples 1-2, 4, 6-7, and 9-13 in the specification for treating specific cancers. In other words, Applicants have amended the claims to recite specific compounds that are effective against four cancer cell lines, for which Applicants have shown

data (specification at p. 100, line 14 and Table 5). Support for the amendments to claims 43 and 50 can also be found in claims 46-47 and claim 52, respectively, as originally filed. Claims 45-47, 52, 54, 56, 60, 62, 68, 70, 76-77 and 84-89 have been cancelled. Therefore, the rejection should be withdrawn.

(2) Rejection of Claims 1-2, 22, 35, and 90-91 under 35 U.S.C. §103(a).

Claims 1-2, 22, 35, and 90-91 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Yamamori, *et al.*, JP 2001-139550 ("Yamamori").

The Examiner alleges that Yamamori "teaches structurally similar compounds." However, the broad genus of Yamamori is not so structurally similar to the claimed compounds that the reference would render Applicants' claims obvious.

The Examiner has failed to identify a single species within the scope of the rejected claims that is taught or suggested by Yamamori, which speaks clearly to the point that the broad genus of Yamamori and the claimed compounds are not so structurally similar that the claimed compounds can be regarded as obvious over Yamamori. Beyond the assertion of "structural similarity" the Examiner has failed to identify any reason why the skilled person would modify Yamamori to obtain compounds within the scope of each of the rejected claims.

It is respectfully submitted that it is clear that the Examiner has not established a *prima facie* case of obviousness. A *prima facie* case of obviousness, in addition to showing the differences between the prior art reference and the claimed invention, must establish the reasons why the claimed invention would have been obvious, that is, why a skilled person would be led to modify the teachings of the reference to provide the claimed invention. MPEP 2141.III and 2142. Applicants point out that in a recent case decided at the Federal Circuit, a patent was held not invalid since there was no evidence of a *prima facie* case of obviousness based on a structurally similar compound because there was no motivation in the prior art for selection of that earlier ("structurally similar") compound. The Federal Circuit cautioned that in view of *KSR Int'l Co. v. Teleflex Inc.* ("*KSR*"), 550 U.S. ___, 82 USPQ2d 1385 (2007), it is not "obvious to

try" one out of a multitude of compounds if there is no reasonable expectation of success (*Takeda v. Alphapharm*, 492 F.3d 1350, 1360, 83 USPQ.2d 1169 (Fed. Cir., 2007) ("the court found nothing in the prior art to narrow the possibilities of a lead compound to compound b.")). In the *Takeda* opinion, the court contrasted their finding in *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir., 2007) ("ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, ...") *Id.* at 1360. In the present case, nothing in the prior art would lead a skilled person to modify the teachings of Yamamori to arrive at either the claimed genus of claim 1, or the more narrow genus of amended claim 8 (as discussed below).

The English abstract of Yamamori demonstrates that an enormous diversity of compounds fall within formula I, which would not have obviously led to the instant claimed invention. It appears to be clear that the Examiner has used the Applicants' own teachings to make the appropriate selections in the generic formula set forth by Yamamori. However, the use of hindsight is not appropriate to establish why the presently claimed invention would have been obvious to the person skilled in the art at the time the presently claimed invention was made. The MPEP makes clear that a *prima facie* case of obviousness must be established based on the reference itself unguided by the Applicants' disclosure, *i.e.* obviousness is determined looking forward from the reference, not backward from the claimed invention. Again, there is no teaching nor suggestion in Yamamori that would lead one of ordinary skill in the art to select the claimed compounds.

Looking to the untranslated Yamamori patent document itself, insofar as it is understood by Applicants, the Examiner has not stated a reason it would have been obvious to modify any of the compounds taught in the reference to make compounds within the scope of the rejected claims. Applicants have set forth their assumptions concerning the content of the untranslated document in Applicants' response to office action mailed April 13, 2007, pp. 63-67. Notably, the essential features of the compounds of instant claim 1 appear infrequently in the compounds described in Yamamori, and do not appear together at all in *any* of the compounds of Yamamori.

In the present Office Action on page 4, the Examiner states: "Inasmuch the reference have made compounds having OH and OMe substituents, they are indeed equivalent." As this statement applies to the A ring of Yamamori, and since R² in current claim 1 has been amended to exclude OH, this issue appears to be moot.

Therefore, considering Yamamori as a whole, it is respectfully submitted that a person skilled in the art who wished to make more compounds with similar properties to those described by Yamamori would make compounds that had the features that are represented most frequently in the compounds that Yamamori made, as these would be assumed to be the features that impart the desired effectiveness to the compounds for treating arteriosclerosis. For example, it appears from Yamamori that for Ar¹, unsubstituted rings, particularly 2-pyridyl are strongly preferred, while for ring A of Yamamori, unsubstituted or monosubstituted rings are preferred. The person skilled in the art would therefore be led to make compounds with these features rather than features which would lead to compounds within the scope of the rejected claims. The data given on p. 38 of Yamamori (untranslated) reinforce this conclusion, showing that compound Ia-39 (having Ar¹=2-pyridyl and A=4-chlorophenyl) is the most potent compound for which data is presented.

Based on the foregoing, the Examiner has failed to establish a *prima facie* case of obviousness against claim 1 or the rejected claims depending therefrom. The Examiner is relying on the Yamamori publication, and no translation has been provided, nor the reasons why a skilled person would be led to modify the reference. It is incumbent on the Examiner to provide reasons why the skilled person would modify the Yamamori reference to provide the claimed invention in order to establish a *prima facie* case of obviousness.

Applicants have amended claim 8 to read on the elected species, and request that this claim, withdrawn but currently amended, be rejoined for examination pursuant to MPEP 821.04 for the purpose of advancing prosecution. (Claims 11, 15-16, 18-19, 21 and 83, depending from claim 8, should also be rejoined.) Specifically, the term "R^{3m}" has been expanded to include the group "-OR⁴ⁿ" on ring A, which finds support in the specification at p. 19, line 20, which names

the elected species in describing the claimed embodiment, and in claim 1 as originally filed. Applicants also point to another described example supporting claim 8, namely (*E*)-*N*-(4-methoxy-3-aminophenyl)-3-(2,4,6-trimethoxyphenyl)-2-propenamide at p. 21, line 19, which differs from the elected species only in the substitution of a 3-amino group on ring A. It would be readily evident to a skilled person that the geometries defined in amended claim 8 not only read on compounds having a 3-amino group on ring A, but also read on compounds having a 3-OR⁴ group on ring A, which includes the elected species.

As discussed above, Yamamori discloses that for Ar¹, unsubstituted rings, particularly 2-pyridyl are strongly preferred, while for ring A of Yamamori, unsubstituted or monosubstituted rings are preferred. These are the primary structural characteristics of the compounds of Yamamori. There is no discussion in Yamamori of the claimed angular relationships between the substituents of Ar¹ (aniline-type) and the rest of the molecule, as for the corresponding substituents of ring A in amended claim 8, nor a requirement for 2 or 3 substituents on Ar¹, as for the corresponding substituents of ring A in amended claim 8. In fact, Yamamori discloses only two compounds having two substituent groups on the Ar¹ ring (aniline-type), corresponding to the claimed A ring (aniline-type) of the claimed invention, and Yamamori does not disclose any compounds having three substituent groups on the Ar¹ ring. In contrast, amended claim 8 is directed to compounds having two or three substituent groups on the A ring (aniline-type) in a specific geometric configuration. Furthermore, neither of the two Yamamori compounds (Ia-2 and Ia-10) include a para- substituent as claimed. In other words, the claimed A ring (aniline-type) is at least para-, meta- di-substituted, while in contrast, Yamamori generally teaches compounds that are unsubstituted on the corresponding Ar¹ ring. Therefore, claim 8 as amended cannot be rendered obvious by Yamamori, and should be allowable.

New claims 92 and 93 (elected species) depend from amended claim 8, and should be allowable, since the claimed geometric relationships of both groups R^{3p} and R^{3m} to the -N(R¹)-C(=X)-CH=CH-B-R² moiety of formula I are not found in Yamamori. The new claims are directed to specific compounds, supported by Examples 3-10 and 11 (elected species), respectively, in the specification, taken from claim 22 as originally filed.

Furthermore, in the Office Action of April 13, 2007, on p. 9, the Examiner indicated that the elected species is allowable and that claims readable on the elected species and closely related compounds would be allowed, along with the composition and corresponding process claims. The elected species is claimed in new claim 93, which depends from claim 8. Claim 8 is a claim that is commensurate with an allowable scope, in that Applicants have amended claim 8 to include the elected species and other closely related compounds in which the A-ring is at least para-, meta- disubstituted in a particular geometric configuration. Yamamori does not teach such compounds.

Furthermore, new claim 94, depending from amended claim 83 (which ultimately depends from claim 8), has been added directed to specific compounds taken from claim 22 as originally filed, and should be allowable for the same reasons discussed above. In particular, these claimed compounds, and nothing remotely like them are disclosed in Yamamori.

It is respectfully submitted that since the Examiner has failed to establish *prima facie* obviousness of claims 1-2, 22, 35 and 90-91, the rejection should be withdrawn.

(3) Rejection of Claims 24-25 under 35 U.S.C. §103(a).

Claims 24-25 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,705,521 to Abraham, *et al.* ("Abraham").

Applicants respectfully point out that the Examiner has failed to establish a *prima facie* case of obviousness. In claims 24-25, Applicants are claiming a method of making particular amides using particular starting materials. In order to establish a *prima facie* case of obviousness, the Examiner is required to clearly articulate the reasons why a skilled person would modify Abraham to perform the method steps of the rejected claims. Abraham does not teach or suggest the desirability of making such a modification. Furthermore, the Examiner has not given any other reason for making such a modification to Abraham, except that the processes disclosed in Abraham are "similar to those claimed," which is not sufficient reason for making a modification under MPEP 2143.C. Applicants also point out that since R² in current claim 8 has

been amended to exclude OH, the method shown in Figure 25 of Abraham, which requires OH on the phenyl group, cannot render the claims obvious.

In the Office Action of September 5, 2007 on page 6, the Examiner indicates that if the compounds are patentable, the process of making the compounds is patentable. Applicants' understanding is that if the rejections of claims 1-2, 22, 35 and 90-91 are removed, then claims 24-25 will be patentable. Based on Applicants' arguments in sections (2) and (3), therefore, the obviousness rejection of claims 24-25 should be withdrawn.

Applicants' comments in support of patentability of the rejected claims made in response to the office action would apply with full force to the claims as presently herein amended.

Applicants respectfully submit that upon entry of the presently submitted response, the application would be placed in condition for allowance. Applicants therefore respectfully solicit the entry of the submitted amendment and issuance of a notice of allowance.

Respectfully submitted,

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